REMARKS

Claims 7-9 and 13-25 were pending in the subject application. By this Amendment, applicants have amended claims 7, 8, 13 and 20 to more clearly recite the claimed invention. Applicants note that the amendments are fully supported in the specification at, *inter alia*, page 60, lines 7-24. Thus, applicants maintain that these amendments do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 7-9 and 13-25, as amended, will be pending and under examination.

Applicants thank the Examiner for the courtesy extended during the telephone interview with John P. White, Esq. on June 7, 2006. During the June 7, 2006 interview, Examiner Jeffrey Parkin alleged that the pending claims are not supported by an adequate written description because the specification lacks structural and/or functional limitations of the molecular determinants modulating the binding interaction between the agent and the target.

Rejections under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner maintained the rejection of claims 7-9 and 13-25 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner indicated that applicants fail to provide any objective scientific data addressing the structural and/or functional constraints which govern the selection of agents in the claimed methods. The

Examiner also alleged that the molecular determinants modulating HIV-1 envelope fusion are complex (citing O'Brien et al. 1990). The Examiner alleged that the description provides a generic screening assay for identifying putative macrophage-tropic-specific or T-cell-tropic-specific inhibitors, but fails to provide any guidance pertaining to the structure of those compounds that can reasonably be expected to inhibit viral cell fusion. The Examiner alleged that the skilled artisan cannot reasonably predict the structure of any given inhibitor. Furthermore, the Examiner alleged that although four monoclonal antibodies capable of inhibiting envelope-mediated viral cell fusion, none of these compounds are specific to either macrophage-tropic or T-cell tropic isolates. The Examiner alleged that nothing in the disclosure directs the skilled artisan toward any particular class of agents. Applicants note that the Examiner has repeated the grounds of rejection which applicants have already addressed in their February 10, 2006 Amendment. Nevertheless, in response, applicants respectfully traverse the Examiner's ground of rejection for the reasons set forth below.

Applicants maintain that the binding specificity of the agent and its preferential inhibitory activities, i.e., that the agent inhibits fusion of HeLa-env_{JRFL} to a PM1 cell, but does not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, as recited in the pending claims, are functionally identifying characteristics of the agent. Applicants maintain that the specification discloses that each of monoclonal antibodies PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell (see page 60, lines 13-16 and Table 3), but does not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell (see Table 3). Applicants further maintain that the binding of the agent to a particular type of target cell is itself a function of the agent. Moreover, there is a correlation between the function of the agent and the

preferential inhibition of the agent.

In addition, applicants note that the specification discloses and exemplifies a routine, reproducible RET assay for identifying an agent which inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell, but does not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, as recited in the pending claims. Accordingly, suitable agents can be identified on the basis of results of the RET screening assay. Applicants further note that the specification provides working examples of agents that satisfy the requirements recited in the pending claims, namely monoclonal antibodies and β-chemokines. Specifically, the specification discloses the PA-3, PA-5, PA-6 and PA-7 monoclonal antibodies as examples of agents that meet the requirements of the agent as recited in the claims, as well as the β-chemokines, RANTES, MIP-1α and MIP-1β (see Table 4 on page 63 of the specification).

Applicants further disagree with the Examiner's statement that "[w]hile the disclosure describes the isolation of four Mabs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T cell-tropic isolates." In this regard, applicants direct the Examiner's attention to the experimental data demonstrating that each of PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell (see the specification at page 60, lines 13-16 and page 61, Table 3), but does <u>not</u> inhibit fusion of HeLa-env_{LAI} to a <u>HeLa-CD4+ cell</u> (see Table 3).

Applicants note that the claimed invention recites the use of an agent which does not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Applicants maintain that it is not fusion of HeLa-env_{LAI} to <u>any</u> CD4+ cell that the agent does not inhibit, but rather, it is fusion to a <u>HeLa-CD4+ cell</u>. Applicants respectfully direct the

Examiner's attention to page 61, Table 3 in the specification, which shows that PA-3, PA-5 and PA-7 inhibited fusion of HeLa-env_{LAI} to HeLa-CD4+ cells by 0%, and PA6 inhibited by a de minimis 7.7%. By comparison, PA-3, PA-5 and PA-6 inhibited fusion of HeLa-env_{JR-FL} to HeLa-CD4+ cells by 85, 96 and 92%, respectively, and PA7 inhibited by 67%. Thus, contrary to the Examiner's assertions, applicants maintain that the fusion-inhibitory activity of PA-3, PA-5, PA-6 and PA-7 demonstrates and meets the requirements of the pending claims. Applicants note that the HeLa-env_{JR-FL} and HeLa-env_{LAI} cell lines used in the RET assay represent the fusion activity of macrophage-tropic and T cell-tropic HIV-1 strains, respectively (see the specification at, *inter alia*, page 52, lines 11-33 and pages 57-59).

In addition, applicants have previously submitted a Declaration Under 37 C.F.R. §1.132 Of Tatjana Dragic in connection with a related application, U.S. Application Serial No. 09/460,216 (the '216 application). A copy of the Declaration is attached hereto as **Exhibit A**. Dr. Dragic's qualifications are listed in her *Curriculum vitae* attached to the Declaration as **Exhibit 1**.

In the attached Declaration, Dr. Dragic states that one of skill in the art could have readily, without the need for a significant amount of experimentation, have utilized the above-referenced RET assay for determining whether any given nonpeptidyl agent inhibits the fusion of HIV-1 or an HIV-1 infected cell to a CD4+ cell. Such an agent can then be used to inhibit the fusion of HIV-1 or an HIV-1 infected cell to a CD4+ cell. As evidence of knowledge of such RET assays in the art, Dr. Dragic attached as **Exhibit 2** of the Declaration a copy of PCT International Publication No. WO/16789 entitled "Methods For Using Resonance Energy Transfer-Based Assay Of HIV-1 Envelope Glycoprotein-Mediated Membrane Fusion, And Kits For Practicing The Same", published June 22, 1995.

Dr. Dragic also states that the specification of the '216 application provides substantial disclosure and a significant degree of guidance as to the use of RET assays for determining the presence of cell fusion. Such RET assays are, as previously noted, well-understood, and provide reliable and reproducible results which are readily capable of being practiced by one of ordinary skill in the art.

Dr. Dragic cites to specific teachings of the specification of the '216 application. Applicants assert that these teachings are also disclosed in the subject application. For example, Dr. Dragic cites to page 1, line 32 to page 2, line 2, of the '216 application as teaching that a RET assay offers a significant advantage in the art in determining whether compounds, including chemokines, differentially inhibit fusion mediated by the envelope glycoprotein from the primary macrophage-tropic isolate of HIV-1_{JR-FL}, compared with fusion mediated by the envelope glycoprotein from HIV-1_{LAI}, a laboratory adapted T lymphotropic strain of HIV-1. Dr. Dragic also cites to page 3, lines 1-7, as teaching the use of the RET assay for identifying non-chemokines, which, according to the teaching of the application, inhibit HIV-1 envelope glycoprotein mediated membrane fusion and thereby neutralize the HIV-1 virus without producing an inflammatory response. Applicants maintain that these passages reflect the teaching of the present application as described hereinabove and generally in the Second Series of Experiments on pages 51-64 of the subject application.

In the attached Declaration, Dr. Dragic further states that the specification of the '216 application provides, at page 5, line 28, to page 6, line 7, a description of the RET assay for use in determining whether an non-chemokine agent inhibits the fusion of HIV-1 to a CD4+ cell. Applicants maintain that such a

description may be found in the subject application at page 19, lines 12-32. Dr. Dragic also points to Table 2 of the '216 application as an example of the use of the RET assay to identify the effect of β-chemokines on HIV-1 envelope glycoprotein-mediated membrane fusion. Applicants contend that the results in Table 2 of the '216 application may be found in Table 4 on page 63 of the subject application.

In addition, on page 6 of the attached Declaration, Dr. Dragic asserts that it is not necessary for one skilled in the art to know in advance the structure of the agent. Dr. Dragic asserts that this concept is clearly demonstrated by the disclosure contained in the Abstract of W. Olson et al. entitled "Identification of CCR5 Coreceptor Inhibitors That Potently And Selectively Block HIV-1 Replication". A copy of the Abstract is attached to the Declaration as **Exhibit 3**.

In summary, on page 7 of the attached Declaration, Dr. Dragic declares that even without prior knowledge of the compounds sought, but with knowledge of their desired use, one of ordinary skill in the art, relying upon the detailed teachings and guidance concerning the RET assay provided in the specification of the '216 application (which applicants contend, as stated above, may also be found in the specification of the subject application), can readily determine the desired agents without undue experimentation.

In view of the above remarks, applicants maintain that the subject specification provides a sufficient and adequate description commensurate with the scope of the pending claims. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the ground of rejection set forth in the May 2, 2006 Final Office Action, and request allowance of pending claims 7-9 and 13-25 in the subject application.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the PTO-1449 (substitute) form attached hereto as **Exhibit B.**

In accordance with 37 C.F.R. §1.92(a)(2)(ii), copies of the U.S. Patents and U.S. Patent Application Publications listed herein are not provided. Accordingly, copies of documents listed below as items 1-32 are not submitted herewith. Copies of documents listed below as items 33-59 are attached hereto as **Exhibits 1-27.**

1. U.S. Patent No. 6,025,154 issued October 10, 2004 to Y. Li et al.;

2. U.S. Patent No. 6,511,826 issued January 28, 2003 to Y. Li et al.;

3. U.S. Patent No. 6,743,594 issued June 1, 2004 to Y. Li et al.;

4. U.S. Patent No. 6,800,729 issued October 5, 2004 to Y. Li et al.;

5. U.S. Patent No. 5,449,608 issued September 12, 1995 to N. Young et al.;

6. U.S. Patent No. 5,126,433 issued December 21, 1989 to P.J. Maddon et al.;

7. U.S. Patent No. 5,021,409 issued June 4, 1991 to B.A. Murrer et al.;

8. U.S. Patent No. 5,440,021 issued August 5, 1995 to A. Chuntharapai et al.;

9. U.S. Patent No. 5,504,003 issued April 2, 1996 to H. Li et al.;

10. U.S. Patent No. 5,071,964 issued December 10, 1991 to M. Dustin et al.;

11. U.S. Patent No. 5,091,513 issued February 25, 1992 to J. Huston et al.;

12. U.S. Patent No. 5,215,913 issued June 01, 1993 to M.R. Posner et al.;

13. U.S. Patent No. 5,225,539 issued July 06, 1993 to G.P. Winter et al.;

14. U.S. Patent No. 5,603,933 issued February 18, 1997 to V.A. Dwyer et al.;

15. U.S. Patent No. 5,668,149 issued September 16, 1997 to S. Oroszlan et al.;

16. U.S. Patent No. 5,854,400 issued December 29, 1998 to T. Chang et al.;

17. U.S. Patent No. 4,886,743 issued December 12, 1989 to L.E. Hood et al.;

18. Y. Li et al., U.S. Patent Application Publication No. 2003-0023044 published January 30, 2003;

19. P.W. Gray et al., U.S. Patent Application Publication No. 2005-0260565 published November 24, 2005;

20. P.W. Gray et al., U.S. Patent Application Publication No. 2005-0118677 published June 2, 2005;

21. P.W. Gray et al., U.S. Patent Application Publication No. 2002-0150888 published October 17, 2002;

22. P.W. Gray et al., U.S. Patent Application Publication No. 2004-0230037 published November 18, 2004;

23. Y. Li et al., U.S. Patent Application Publication No. 2004-0151719 published August 8, 2004;

24. Y. Li et al., U.S. Patent Application Publication No.2001-0000241 published April 12, 2002;

25. W.C. Olson et al., U.S. Patent Application Publication No. 2002-0106374 published August 8, 2002;

26. W.C. Olson et al., U.S. Patent Application Publication No. 2002-0146415 published October 10, 2002;

27. W.C. Olson et al., U.S. Patent Application Publication No. 2003-0044411 published March 6, 2003;

28. G.P. Allaway et al., U.S. Patent Application Publication No. 2006-0029932 published February 9, 2006;

29. G.P. Allaway et al., U.S. Patent Application Publication No. 2004-0086528 published May 06, 2004;

30. G.P. Allaway et al., U.S. Patent Application Publication No. 2006-0140977 published June 29, 2006;

31. G.P. Allaway et al., U.S. Patent Application Publication No. 2006-0233798 published October 19, 2006;

32. G.P. Allaway et al., U.S. Patent Application Publication No. 2006-0194244 published August 31, 2006;

33. W.C. Olson et al., U.S. Patent Application Serial No. 11/316,078 filed December 21, 2005 **(Exhibit 1)**;

34. G.P. Allaway et al., U.S. Patent Application Serial No. 11/258,963 filed October 25, 2005 **(Exhibit 2)**;

35. V.M. Litwin et al., U.S. Patent Application Serial No. 08/587,458 filed January 17, 1996 (now abandoned) **(Exhibit 3)**;

36. G.P. Allaway et al., U.S. Patent Application Serial No. 08/663,171 filed June 14, 1996 (now abandoned) **(Exhibit 4)**;

37. W.C. Olson et al., U.S. Patent Application Serial No. 09/594,983 filed June 15, 2000 **(Exhibit 5)**;

38. W.C. Olson et al., U.S. Patent Application Serial No. 09/663,219 filed September 15, 2000 **(Exhibit 6)**;

39. W.C. Olson et al., U.S. Patent Application Serial No. 09/464,902 filed December 16, 1999 **(Exhibit 7)**;

40. W.C. Olson et al., U.S. Patent Application Serial No. 11/581,944 filed October 16, 2006 **(Exhibit 8)**;

41. W.C. Olson et al., U.S. Patent Application Serial No. 11/581, 945 filed October 16, 2006 **(Exhibit 9)**;

42. W.C. Olson et al., U.S. Patent Application Serial No. 11/520,556 filed September 12, 2006 **(Exhibit 10)**;

43. V.M. Litwin et al., U.S. Patent Application Serial No. 11/544,346 filed October 5, 2006 **(Exhibit 11)**;

44. PCT International Application Publication No. WO 92/01451 published February 06, 1992 **(Exhibit 12)**;

45. PCT International Application Publication No. WO 96/39437 published December 12, 1996 **(Exhibit 13)**;

46. PCT International Application Publication No. WO 94/22477 published October 14, 1994 **(Exhibit 14)**;

47. Alexander, H. et al., (1992) "Altering The Antigenicity Of Proteins", *Proc. Natl. Acad. Sci.* 89:3352-3356 **(Exhibit 15)**;

48. Frazer, J.K. and Capra, J.D., (1999) "Immunoglobulins: Structure And Function" Fundamental Immunology, 4th Edition, Lippincott-Raven Publishers, Philadelphia, Pp. 37-74 **(Exhibit 16)**;

49. Mateu, M.G. et al. (1992) "Non-Additive Effects Of Multiple Amino Acid Substitutions On Antigen-Antibody Recognition", *European J. Immunol.* 22(6):1385-1389 **(Exhibit 17)**;

50. Max, E., "Immunoglobulins: Molecular Genetics" Fundamental Imunology, 4th Edition. Lippincott-Raven Publishers, Philadelphia, 1999 Pp. 11-182 **(Exhibit 18)**;

51. Tilley, S. A. (1992) "Synergistic Neutralization Of HIV-1 By Human Monoclonal Antibodies Against The V3 Loop And The CD4-Binding Site gp120", *AIDS Research And Human Retroviruses* 80:4:461-467 **(Exhibit 19)**;

52. Vanini, S. et al., (1992) "Discrete Regions Of HIV-1 gp41 Defined By Syncytia-Inhibiting Affinity-Purified Human Antibodies", *AIDS* 7:167-174 **(Exhibit 20)**;

53. Verrier, F.C. et al., (1997) "Antibodies To Several Conformation-Dependent Epitopes Of gp120/gp41 Inhibit CCR-5-Dependent Cell-To-Cell Fusion Mediated By The Native Envelope Glycoprotein Of A Primary Macrophage-Tropic HIV-1 Isolate", *Proc. Natl. Acad. Sci.* 94:9326-9331 **(Exhibit 21)**;

54. PCT International Search Report Issued March 13, 1995 for International Application Publication No. WO 95/16789 **(Exhibit 22)**;

55. PCT International Preliminary Examination Report issues October 18, 1996 for International Application Publication No. 95/16789 **(Exhibit 23)**;

56. European Supplementary Search Report Issued September 5, 2002 for European Patent Application No. 95905987.4 **(Exhibit 24)**;

57. PCT International Search Report Issued October 10, 1996 for International Application Publication No. WO 96/41020 **(Exhibit 25)**;

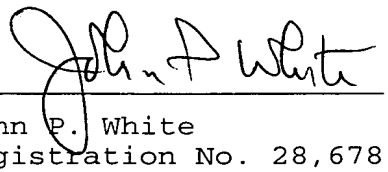
58. PCT International Preliminary Examination Report issued September 5, 1997 for International Application Publication No. WO 96/41020 **(Exhibit 26)**; and

59. European Supplementary Search Report issued February 24, 2000 for European Patent Application No. 96921473.3 **(Exhibit 27)**.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No other fee, other than the $395.00 fee for filing an RCE and the $510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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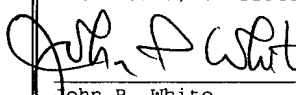

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Date